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(54) Title: TOPICAL TREATMENT OF BLEPHARITIS			
(57) Abstract <p>The object of the invention is to provide a method and composition for treating blepharitis or blepharoconjunctivitis which comprises topical administration of a nitroimidazole compound, e.g. metronidazole in a suitable ophthalmic carrier directly to affected ocular tissues. The carrier can be based on an artificial tear solution, an ointment, a water soluble gel, a nonaqueous carrier or an eyelash shampoo.</p>			

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TOPICAL TREATMENT OF BLEPHARITISCross Reference to Related Applications

This application is a United States of America continuation-in-part application of Serial
5 No. 07/568,461 filed August 16, 1990 for "Topical Treatment of Blepharitis", which is a United States of America continuation-in-part application of Serial No. 07/204,547 filed June 9, 1988 for "Topical Treatment of Blepharitis" by the same
10 inventors in the United States Patent and Trademark Office.

Technical Field

The present invention relates to the field of treating abnormal eye inflammation and more
15 particularly to the topical treatment of inflammations and other dysfunctions of the eyelid and conjunctiva. The present invention is especially concerned with the treatment of meibomian gland dysfunction, blepharitis, and
20 blepharoconjunctivitis particularly associated with ocular rosacea.

Art

Blepharitis is an inflammation of the eyelids. Blepharoconjunctivitis is an
25 inflammation of the eyelids and the conjunctiva of the eye. Both conditions are associated with the condition known as ocular rosacea.

Rosacea is a disease of the skin (acne rosacea) and eyes (ocular rosacea) of unknown
30 etiology and a variety of manifestations. The clinical and pathological features of the eye

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disease are nonspecific, and the disease is widely underdiagnosed by ophthalmologists.

More specifically with respect to ocular rosacea, ocular rosacea may involve the eyelids, conjunctiva, and cornea. Common manifestations of ocular rosacea include blepharitis, blepharoconjunctivitis, meibomianitis, chalazia, styes and conjunctival hyperemia.

References which discuss ocular rosacea include: "Ocular Rosacea" by M.S. Jenkins et al, American Journal of Ophthalmology, Vol. 88:618-622 (1979); "Blepharitis Associates With Acne Rosacea and Seborrheic Dermatitis" by J. P. McCulley et al, in Oculocutaneous Diseases, edited by J. P. Callen et al, Little, Brown & Company, International Ophthalmology Clinics, Spring 1985, Vol. 25, No. 1, pp. 159-172; and "Ocular Rosacea" by D. J. Browning et al, Survey of Ophthalmology, Vol. 31, No. 3, November-December 1986, pp. 145-158.

In the article by McCulley et al mentioned above, on pages 170-172, several treatments for blepharitis are disclosed. These treatments include: topical antibiotics; oral tetracycline; SSA neutralizers; exoenzymatic inhibitors; vitamin A analogs; and other means of affecting meibomian gland secretions.

In another prior art reference, Textbook of Dermatology, 4th Edition, A. Rook et al editors, Vol. 2, p. 3252, there is a disclosure that Demodectic blepharitis may be treated with bathing with boric acid or with benzalkonium chloride.

In the article by Browning et al mentioned above, on p. 155, there is a disclosure that for treatment of ocular rosacea only tetracycline has

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been critically studied. In the same article, there is mentioned that metronidazole has been used for treatment of skin lesions of rosacea. However, the article does not teach the use of a
5 nitroimidazole compound (including metronidazole) with a suitable carrier for topical treatment of ocular tissues.

In another reference, namely "Topical Metronidazole Therapy for Rosacea", by P. A.
10 Bleicher et al, Arch Dermatol., Vol. 123, May 1987, pp. 609-614, there is a disclosure that metronidazole can be used in a gel for treatment of rosacea of the skin. However, there is no disclosure that metronidazole can be used for
15 ocular rosacea.

The prior art also teaches other treatments for eye inflammations using the direct application of a treating composition to the eye. For example, in U.S. Patent 4,612,193 to Gordon et al,
20 there is a disclosure that a blepharitic infection (not characterized as being caused by ocular rosacea) can cause a sty and that an ointment is provided to treat the sty. The ointment is based on yellow mercuric oxide, boric acid, and wheat
25 germ oil.

In the book Diseases of the Cornea, 2nd Edition, by M.G. Grayson, C. Z. Mosby Company, 1983, pp. 119-209, there is a disclosure that blepharitis can be treated using antibiotic
30 ointments containing antibiotics such as bacitracin, erythromycin, chloramphenicol, and tetracycline. Other active agents for treating blepharitis include Rifampin, a very dilute steroid such as 0.12%, prednisolone, and
35 polysulfide.

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The prior art treatments for eye inflammations have several disadvantages. For example, when tetracycline is taken orally it takes between two to three months to have a significant effect. Furthermore, tetracycline is plagued with side effects such as super infections, light sensitivity, cramp feelings of the user, contraindication if the user is pregnant, and resultant feelings that are similar to those when a person has the flu. Therefore, it would be desirable to avoid the use of tetracycline for the treatment of eye inflammations (e.g. ocular rosacea and related conditions).

Another eye condition is known as dry eye which results from an abnormal deficiency of tear production. A discussion of dry eye is found in the article entitled "Tear Physiology and Dry Eyes" by F. J. Holly et al, Survey of Ophthalmology, Vol. 22, No. 2, September-October 1977, pp. 69-87. As disclosed in the Holly et al article, the primary treatment for dry eye is the use of artificial tears applied topically. Unfortunately, blepharitis is often misdiagnosed as dry eye. As a result, treatment with artificial tears is inadequate to cure the patient's problem. It would be desirable to provide a pharmaceutical composition that would treat the actual blepharitis in the instance where the condition was misdiagnosed as dry eye.

Another problem that has received attention in the ophthalmological literature lately is infection by a parasite known as Acanthamoeba hystolytica which particularly plagues users of contact lenses. A particularly devastating

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infection results from this parasite leaving the victim particularly susceptible to blindness in an infected eye. A presently used treatment for Acanthamoeba is a therapeutic agent known as
5 brolene which is an over-the-counter British styel medication. Other known treatments for Acanthamoeba include antibiotics such as micadasol and mediasforan. However, it would be desirable if another non-antibiotic agent could be applied
10 topically to alleviate the deleterious conditions caused by the Acanthamoeba organism.

Another problem associated with wearers of contact lenses is the formation of film and deposits on the surface of the lenses. Lumpy
15 deposits formed on the contact lenses are very often due to undiagnosed blepharitis. By alleviating the underlying blepharitis condition, the cause of deposit formation on contact lenses could be alleviated or removed. In this respect,
20 it would be desirable to provide a treatment to prevent deposit formation on contact lenses that result from undiagnosed blepharitis.

The aforementioned contact lens surface film and deposits caused by blepharitis are associated
25 with the formation of bumps (giant papillae) under the upper lids of contact lens wearers. This condition, giant papillary conjunctivitis (GPC), is an immune-mediated reaction to contact lens surface contamination and may require patients to
30 discontinue contact lens wear. By alleviating the underlying blepharitis condition, the cause of the contamination which leads to GPC could be alleviated. This treatment may then allow certain wearers of contact lenses to resume use.

35 Still another option of the invention is to

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provide a treatment to prevent the development of the condition known as giant papillary conjunctivitis (GPC).

Although systemic treatments for eye conditions are known, such treatments are not popular with ophthalmologists. An eye doctor generally prefers to prescribe an eye medicine that is administered topically to the eye rather than prescribe a pill or the like which administers the medicine systemically. Therefore, it would be desirable to provide a treatment for blepharitis, or blepharoconjunctivitis, or ocular rosacea generally that is administered in a form such as a topically applied ointment or topically applied drops.

Disclosure of Invention

Accordingly, it is an object of the present invention to alleviate the disadvantages and deficiencies of the prior art by providing a treatment for meibomian gland dysfunction, blepharitis, blepharoconjunctivitis, and ocular rosacea that is administered in the form of eye drops or other topically administered eye preparations.

Another object of the invention is to provide a treatment that avoids the use of systemic tetracycline or other systemic antibiotics for treating ocular inflammations such as ocular rosacea and related conditions.

Another object of the invention is to provide a pharmaceutical composition that treats actual blepharitis in an instance where the actual condition is misdiagnosed as dry eye.

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Still another object of the invention is to provide a topical treatment for the eye conditions resulting from infection by Acanthamoeba hystolytica.

5 Yet another object of the invention is to provide a treatment to prevent deposit formation on contact lenses that result from undiagnosed blepharitis and related giant papillary conjunctivitis (GPC).

10 In accordance with the teachings of the present invention, a pharmaceutical composition is provided for treating blepharitis and blepharoconjunctivitis generally and especially associated with ocular rosacea. The
15 pharmaceutical composition of the invention includes an amount of nitroimidazole compound effective for treating the blepharitis and/or blepharoconjunctivitis and/or ocular rosacea; and a carrier for the nitroimidazole compound wherein
20 the carrier is suitable for direct application to the eye tissues. The nitroimidazole compound is selected from the group consisting of metronidazole, nimorazole, tinidazole, ordinidazole, secnidazole, and carnidazole. The
25 preferred compound is metronidazole.

The carrier may be in the form of an ointment, e.g. petrolatum-based or a water soluble gel, or in the form of a liquid to be applied to the eye in the form of eye drops. The eye drops
30 can be in a bottle containing a plurality of doses or can be in a unidose dispenser.

One carrier for eye drops is an artificial tear composition including primarily isotonic sodium chloride. Other artificial tear ophthalmic
35 carriers for the eye drops can be a hypertonic

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composition or a hypotonic composition based on sodium chloride solution. Moreover, other hypertonic, isotonic, and hypotonic carriers can be used. In addition, a cellulose ether such as
5 methylcellulose may be added to the artificial tear carrier. Other cellulose ethers such as hydroxypropylmethylcellulose and hydroxyethylcellulose may be included in the artificial tear
10 composition may also include a polyvinyl alcohol.

Another carrier administered in the form of eye drops can have a nonaqueous liquid base, e.g. a mineral oil based carrier. For example, the liquid ocular lubricant LIPO-TEARS, which contains
15 a blend of mineral oil and white petrolatum U.S.P., can be used. The carrier LIPO-TEARS is made by Spectra Pharmaceutical Services, Inc., Hanover, Massachusetts 02339.

Yet another carrier for ocular administration
20 of the nitroimidazole compound is a suspension of solid particles in a liquid. More specifically, the ocular administration can be in the form of an aqueous suspension. Even more specifically, a carrier for administering the nitroimidazole in
25 suspension form can be particles of an ion-exchange resin, e.g. Amberlite, suspended in water. Employment of the ion-exchange resin Amberlite in an aqueous suspension for ocular administration of a betaxolol HCl treating agent
30 (a beta-adrenergic blocker) for treating glaucoma is embodied in BETOPIC®S made by Alcon Laboratories, Inc., Fort Worth, Texas 76134.

The composition of the invention is applied to ocular tissues directly for treating the
35 conditions of blepharitis, blepharoconjunctivitis,

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and ocular rosacea.

Another carrier for the nitroimidazole compound can be a shampoo formulation. In this respect, the nitroimidazole compound can be part
5 of an eyelash shampoo or eyescrub for cleansing hair associated with the eye. Other carriers for the metronidazole compounds can be slow release inserts, aerosols, collagen shields, bandage contact lenses, and contact lens solutions.

10 In yet another aspect of the invention, the nitroimidazole compound can be used in conjunction with a shampoo formulation intended to be used on the scalp areas. This formulation can be used for treating rosacea of the scalp or for hair or fur
15 infestations of Demodex follicularum (mange).

These and other objects and advantages of the present invention will become apparent from a reading of the following specification.

Mode for Carrying Out the Invention

20 Here are represented several formulations for pharmaceutical compositions of the invention.

Example 1

One gram of metronidazole is added to 1,000 grams of artificial tear carrier with stirring.
25 The artificial tear carrier is isotonic sodium chloride solution. This formulation provides an approximately 0.1% solution of metronidazole in artificial tear carrier for application to the patent by means of eye drops.

30 Example 2

One gram of metronidazole is added to 1,000

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grams of artificial tear carrier with stirring. The artificial tear carrier is hypertonic sodium chloride solution. This formulation provides an approximately 0.1% solution of metronidazole in artificial tear carrier for application to the patent by means of eye drops.

Example 3

One gram of metronidazole is added to 1,000 grams of artificial tear carrier with stirring. The artificial tear carrier is hypotonic sodium chloride solution. This formulation provides an approximately 0.1% solution of metronidazole in artificial tear carrier for application to the patent by means of eye drops.

Example 4

7.5 grams of metronidazole are added to 992.5 grams of artificial tear solution with stirring to provide a formulation containing approximately 0.75% metronidazole in an artificial tear carrier.

Example 5

10 grams of metronidazole are added to 990.0 grams of isotonic sodium chloride solution with stirring to provide a 1% metronidazole solution in isotonic sodium chloride carrier.

Example 6

An eye drop formulation is made up by blending the following: 10 grams metronidazole, 10 grams methylcellulose, and 980 grams isotonic

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sodium chloride. This formulation contains approximately 1% metronidazole, 1% methylcellulose, and the balance being isotonic sodium chloride carrier.

5 Example 7

Another eye drop formulation is made up by blending the following: 10 grams, 14 grams polyvinyl alcohol, and 976 grams isotonic sodium chloride artificial tear solution. The resulting
10 formulation contains approximately 1% metronidazole, 1.4% polyvinyl alcohol, and the balance being artificial tear carrier.

Example 8

Another eye drop formulation is made by
15 blending the following: 15 grams metronidazole and 985 grams of isotonic sodium chloride artificial tear solution with stirring to provide a 1.5% metronidazole solution.

Example 9

20 Another eye drop formulation is made by stirring 20 grams metronidazole into 980 grams of artificial tear solution to provide a 2.0% metronidazole solution.

In addition to the artificial tear carriers
25 disclosed above, an artificial tear carrier for the nitroimidazole compound can be selected from an artificial tear formulation selected from the formulations set out in Table I below.

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TABLE I

	<u>Major Component</u>	<u>Trade Name</u>	<u>Preservative</u>
5	Hydroxyethyl-cellulose	Clerz	thimerosal + edetate disodium
		Lyteers	benzalkonium chloride + edetate disodium
10		Teargard	thimersal + edetate disodium
15	Hydroxypropyl-cellulose	Lacrisert* (Water soluble insert)	benzalkonium chloride + edetate disodium
	Hydroxypropyl methycellulose	Isopto Alkaline	benzalkonium chloride
20		Isopto Plain	benzalkonium chloride
		Isopto Tears	benzalkonium chloride
		Lacril	chlorobutanol
25		Muro Tears	benzalkonium chloride + edetate disodium
30		Tearisol	benzalkonium chloride + edetate disodium
	Methylcellulose	Methopto	benzalkonium chloride
35		Methulose	benzalkonium chloride
		Murocel	methylparaben & propylparaben

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	Carboxymethyl-cellulose	Celluvisc	preservative free
		Visculose	benzalkonium chloride
5	Polyvinyl alcohol	Aqua Tears	benzalkonium chloride + edetate sodium
10		Liquifilm Tears	chlorobutanol
		Liquifilm Forte	thimerosal + edetate sodium
		Tears Plus	chlorobutanol
15	Polyvinyl alcohol and cellulose ester	aqua-FLOW	benzalkonium chloride + edetate disodium
20		Neo-Tears	thimerosal + edetate disodium
	Polyvinyl alcohol and povidone	Refresh	preservative free
25	Other Polymeric Systems	Adapettes	thimerosal & edetate disodium
		Adsorbotear	thimerosal & edetate disodium
30		Comfort Drops	benzalkonium chloride + edetate disodium
35		Dual Wet	benzalkonium chloride + edetate disodium
		Hypotears	benzalkonium chloride +

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		edetate disodium
5	Tears Naturale	benzalkonium chloride + edetate disodium

More complete descriptions of artificial tear carriers are found in PDR for Nonprescription Drugs, 1990, pages 504-506.

10 Moreover, the TEARS NATURAL[®] is made by Alcon, (6201 South Freeway, Fort Worth, TX 76134) and is comprised of DUASORB[®] (Dextran 70 Hydroxypropyl Methylcellulose) as a water soluble polymeric system with preservatives benzalkonium
15 chloride, 0.01% and Edetate Disodium 0.05% which is disclosed in U.S. Patent No. 4,039,662, incorporated herein by reference.

Example 10

20 The following ointment can be prepared by blending 10 grams of metronidazole thoroughly with 990 grams petrolatum vehicle (an ointment base) to provide an ointment suitable for application to the ocular tissues which contains 1% metronidazole.

25 Example 11

30 The following ointment can be prepared by blending 15 grams of metronidazole thoroughly with 985 grams petrolatum vehicle (an ointment base) to provide an ointment suitable for application to the ocular tissues which contains 1.5% metronidazole.

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Example 12

The following ointment can be prepared by blending 15 grams of metronidazole thoroughly with 980 grams petrolatum vehicle (an ointment base) to provide an ointment suitable for application to the ocular tissues which contains 2% metronidazole.

Other ointments based upon the petrolatum carrier can be selected from the carriers listed below in Table II.

TABLE II

	<u>Trade Name</u>	<u>Composition</u>
	Akwa-Tears (Akorn)	Petrolatum, Liquid Lanolin, Mineral Oil
15	Duolube (Muro)	Sterile ointment containing white petroleum and mineral oil
20	Duratears (Alcon)	Sterile ointment with white petroleum, liquid lanolin, mineral oil, methylparaben and polyparaben
25	Hypotears (Cooper Vision)	Sterile ointment containing white petroleum and light mineral oil
30	Lacri-Lube S.O.P. (Allergan)	Sterile ointment with 42.5% mineral oil, 55% white petrolatum, lanolin, and chlorobutanol

An ophthalmic gel carrier can also be used for administering the nitroimidazole compound directly to ocular tissues. A suitable ophthalmic

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gel carrier is comprised of approximately 10% CARBOPOL 940 (which is a synthetic high molecular weight cross-linked polymer of acrylic acid to impart a high viscosity. A specific formulation of the invention which employs an ophthalmic gel is set forth below in Example 13.

Example 13

An aqueous gel formulation of the invention is obtained by blending approximately 20 grams of metronidazole with approximately 980 grams of an ophthalmic gel carrier containing approximately 0.08 grams of benzalkonium chloride, 0.5 grams of Edetate Disodium, 80 grams of Carbopol 940, and approximately 900 grams of water.

Another ophthalmic gel carrier can be prepared in accordance with the teaching in U.S. Patent No. 4,788,007 incorporated herein by reference. This patent discloses an aqueous aloe vera gel. To obtain a composition for treating blepharitis in accordance with the subject invention, a quantity of metronidazole is added to a quantity of the aloe vera gel. More specifically, to obtain a gel formulation containing approximately 2% metronidazole, approximately 20 grams of metronidazole are blended with approximately 980 grams of the aloe vera gel.

As stated above, a shampoo which carries a nitroimidazole compound can be used for cleansing eyelashes and for treating ocular rosacea, blepharitis, and blepharoconjunctivitis. In Example 14 below, a formulation for an eyelash shampoo which carries the nitroimidazole compound,

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metronidazole, is presented.

Example 14

The following eyelash shampoo can be prepared by adding 20 grams of metronidazole to approximately 1,000 grams of an eyelid cleanser known as I-SCRUBTM made by Spectra Pharmaceutical Services, Hanover, Massachusetts, that contains the following ingredients: PEG-200 Glyceryl Monotallowate, Disodium Laureth Sulfosuccinate, Cocoamido Propyl Amine Oxide, PEG-78 Glyceryl Monococate, Benzyl Alcohol, Disodium Edetate, and Purified Water USP. I-SCRUBTM (without the presence of the subject metronidazole) is disclosed as being suitable for hygienic care of blepharitis. With the added metronidazole, the eyelash shampoo of the invention is effective in treating the blepharitis.

By employing the principles of the invention, numerous objects are realized and numerous benefits are obtained. For example, a pharmaceutical composition is provided to treat blepharitis, blepharoconjunctivitis, and ocular rosacea and is administered in the form of an ointment or in the form of eye drops. The method of treatment of the invention avoids the use of tetracycline for treating ocular rosacea and related conditions. With the invention, a pharmaceutical composition is provided that treats actual blepharitis in the case where the condition is misdiagnosed as dry eye. The invention provides a topical treatment for eye conditions resulting from infection by Acanthamoeba hystolytica. The invention provides a treatment

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to prevent deposit formation on contact lenses that results from blepharitis and related giant papillary conjunctivitis.

Obviously, many modifications may be made
5 without departing from the basic spirit of the present invention. Accordingly, it will be appreciated by those skilled in the art that within the scope of the appended claims, the invention may be practiced other than has been
10 specifically described herein.

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Claims

1. A pharmaceutical composition,
comprising:

an amount of nitroimidazole compound
5 effective to treat blepharitis and
blepharoconjunctivitis in an animal or human
patient; and
an ophthalmic carrier for said
nitroimidazole compound, said carrier suitable for
10 topical application to ocular tissues.

2. The pharmaceutical composition described
in claim 1 wherein said carrier includes an
ointment base suitable for direct application to
the eye.

15 3. The pharmaceutical composition described
in claim 2 wherein said ointment includes a
petrolatum-based vehicle.

4. The pharmaceutical composition described
in claim 1 wherein said carrier includes a water
20 soluble gel.

5. The pharmaceutical composition described
in claim 1 wherein said carrier includes a liquid
suitable for application to the eye in the form of
drops.

25 6. The pharmaceutical composition described
in claim 1 wherein said nitroimidazole compound is
present in a range of 0.1-1% and the balance being
said carrier.

7. The pharmaceutical composition described
30 in claim 1 wherein said nitroimidazole compound is
present in a range of 0.75-1% and the balance
being said carrier.

8. The pharmaceutical composition described
in claim 1 wherein said nitroimidazole compound is

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present in a range of 0.1-2% and the balance being said carrier.

9. The pharmaceutical composition described in claim 1 wherein said nitroimidazole compound is present in a range of 0.75-2% and the balance being said carrier.

10. The pharmaceutical composition described in claim 1 wherein said nitroimidazole compound is selected from the group consisting of metronidazole, nimoranzole, tinidazole, ordinidazole, secnidazole, and carnidazole.

11. The composition described in claim 1 wherein said nitroimidazole compound is metronidazole.

12. The pharmaceutical composition described in claim 1 wherein said carrier includes a nonaqueous liquid base.

13. The pharmaceutical composition described in claim 1 wherein said carrier includes a mineral oil base.

14. The pharmaceutical composition described in claim 1 wherein said carrier includes a blend of mineral oil and petrolatum.

15. The pharmaceutical composition described in claim 1 wherein said carrier includes a suspension of solid particles in a liquid.

16. The pharmaceutical composition described in claim 1 wherein said carrier includes a suspension of an ion-exchange resin in water.

17. The pharmaceutical composition described in claim 1 wherein said ion-exchange resin includes Amberlite.

18. A pharmaceutical composition, comprising:

an amount of nitroimidazole compound

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effective to treat blepharitis and
blepharoconjunctivitis in an animal or human
patient; and

a carrier for said nitroimidazole
5 compound, said carrier suitable for topical
application to ocular tissues, wherein said
carrier includes an artificial tear composition
which is either hypertonic, isotonic, or
hypotonic.

10 19. The pharmaceutical composition described
in claim 18 wherein said artificial tear
composition includes a cellulose derivative.

20 20. The pharmaceutical composition described
in claim 19 wherein said cellulose derivative is a
15 cellulose ether.

21. The pharmaceutical composition described
in claim 20 wherein said cellulose either is
present as approximately 1% by weight of said
artificial tear carrier.

20 22. The pharmaceutical composition described
in claim 19 wherein said cellulose derivative is
selected from the group of cellulose ethers
consisting of methylcellulose,
hydroxypropylmethylcellulose, and
25 hydroxyethylcellulose.

23. The pharmaceutical composition described
in claim 22 wherein said cellulose derivative
includes methylcellulose.

30 24. The pharmaceutical composition described
in claim 18 wherein artificial tear composition
includes polyvinyl alcohol.

25 25. The pharmaceutical composition described
in claim 24 wherein said polyvinyl alcohol is
present as approximately 1.4% by weight of said
35 artificial tear carrier.

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26. A pharmaceutical composition,
comprising:

an amount of nitroimidazole compound
effective to treat blepharitis and
5 blepharoconjunctivitis in an animal or human
patient; and

a hypotonic carrier for said
nitroimidazole compound, said carrier suitable for
topical application to ocular tissues.

10 27. A pharmaceutical composition,
comprising:

an amount of nitroimidazole compound
effective to treat blepharitis and
blepharoconjunctivitis in an animal or human
15 patient; and

a hypertonic carrier for said
nitroimidazole compound, said carrier suitable for
topical application to ocular tissues.

28. A pharmaceutical composition,
20 comprising:

an amount of nitroimidazole compound
effective to treat blepharitis and
blepharoconjunctivitis in an animal or human
patient; and

25 an isotonic carrier for said
nitroimidazole compound, said carrier suitable for
topical application to ocular tissues.

29. A pharmaceutical composition,
comprising:

30 an amount of a nitroimidazole compound
effective to treat blepharitis and
blepharoconjunctivitis in an animal or human
patient; and

a carrier for said nitroimidazole
35 compound, said carrier suitable for topical

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application to ocular tissues, wherein said carrier is a shampoo suitable for cleansing eyelashes.

30. A pharmaceutical composition,
5 comprising:
an amount of a nitroimidazole compound effective to treat rosacea of the scalp in an animal or human patient; and
a carrier for said nitroimidazole
10 compound, said carrier suitable for topical application to scalp tissues, wherein said carrier is a shampoo suitable for cleansing the scalp and hair or fur.

31. A method of treating a human being for
15 blepharitis or blepharoconjunctivitis which comprises administering to said human being an amount of metronidazole applied directly to ocular tissues effective to treat the blepharitis or blepharoconjunctivitis.

- 20 32. A method of treating a human being for blepharitis or blepharoconjunctivitis which comprises administering to said human being an amount of a compound in the class of nitroimidazole compounds applied directly to
25 ocular tissues effective to treat the blepharitis or blepharoconjunctivitis.

33. The method of treating blepharitis or blepharoconjunctivitis described in claim 32 wherein the nitroimidazole compound is selected
30 from the group consisting of metronidazole, nimorazole, tinidazole, ordinidazole, secnidazole, and carnidazole.

34. The method of treating blepharitis or blepharoconjunctivitis described in claim 32

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wherein the nitroimidazole compound is
metronidazole in a range of 0.1-2% by weight.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 90/05173

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : A 61 K 31/415, A 61 K 9/06																	
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">IPC⁵</td> <td style="border: 1px solid black; padding: 5px;">A 61 K</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	IPC ⁵	A 61 K											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; font-size: x-small;">Category ¹⁰</th> <th style="width: 70%; font-size: x-small;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; font-size: x-small;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td style="vertical-align: top;">Arch Dermatol, volume 123, May 1987, P.A. Bleicher et al.: "Topical metronidazole therapy for rosacea", pages 609-614 see the whole document</td> <td style="text-align: center; vertical-align: top;">1-29</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;">cited in the application ---</td> <td style="text-align: center; vertical-align: top;">30</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td style="vertical-align: top;">Survey of Ophthalmology, volume 31, no. 3, November/December 1986, D.J. Browning et al.: "Ocular Rosacea", pages 145-158 see the whole document cited in the application ---</td> <td style="text-align: center; vertical-align: top;">1-29</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td style="vertical-align: top;">Chemotherapy, volume 29, 1983, A. Karger AG, (Basel, CH), J. Mattila et al.: "Penetration of metronidazole and trinitidazole into the aqueous humor in man", pages 188-191 see the whole document ---</td> <td style="text-align: center; vertical-align: top;">1-29</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	Y	Arch Dermatol, volume 123, May 1987, P.A. Bleicher et al.: "Topical metronidazole therapy for rosacea", pages 609-614 see the whole document	1-29	X	cited in the application ---	30	Y	Survey of Ophthalmology, volume 31, no. 3, November/December 1986, D.J. Browning et al.: "Ocular Rosacea", pages 145-158 see the whole document cited in the application ---	1-29	Y	Chemotherapy, volume 29, 1983, A. Karger AG, (Basel, CH), J. Mattila et al.: "Penetration of metronidazole and trinitidazole into the aqueous humor in man", pages 188-191 see the whole document ---	1-29
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%; font-size: x-small;"> <p>¹⁴ Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 50%; font-size: x-small;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"G" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> Date of the Actual Completion of the International Search <div style="text-align: center; padding-top: 10px;">19th April 1991</div> </td> <td style="width: 50%; border: none;"> Date of Mailing of this International Search Report <div style="text-align: center; padding-top: 10px;">12.06.91-</div> </td> </tr> <tr> <td style="width: 50%; border: none;"> International Searching Authority <div style="text-align: center; padding-top: 10px;">EUROPEAN PATENT OFFICE</div> </td> <td style="width: 50%; border: none;"> Signature of Authorized Officer <div style="text-align: center; padding-top: 10px;"> Mme Dagmar FRANK </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; padding-top: 10px;">19th April 1991</div>	Date of Mailing of this International Search Report <div style="text-align: center; padding-top: 10px;">12.06.91-</div>	International Searching Authority <div style="text-align: center; padding-top: 10px;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center; padding-top: 10px;"> Mme Dagmar FRANK </div>											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, " with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WO, A, 8906537 (CURATEK PHARMACEUTICALS) 27 July 1989 see abstract; claims	1-29
X	---	30
A	FR, A, 2624736 (DIETLIN F.) 23 June 1989 see abstract; claims	1-30
A	---	
A	US, A, 4612193 (GORDON et al.) 16 September 1986 see abstract; column 1, lines 16-27; claims cited in the application	2,3,12-14
A	---	
A	FR, A, 2333500 (ALCON LABS.) 1 July 1977 see page 1, lines 1-28; page 5, lines 7-30; claims cited in the application	5,18-25

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

incompletely

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 31-34, because they relate to subject matter not required to be searched by this Authority, namely:

Pls. see Rule 39.1 (iv) - PCT:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☒ Claim numbers XX, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

xx Claims searched incompletely 1-9; 12-30

Reason: Arit. 6 PCT:

(The claim or claims shall define the matter for which protection is sought. Claims shall be clear and concise. They shall be fully supported by the description.) The expression "nitroimidazole compound" gives no exact and accurate definition for a chemical compound.

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This international Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9005173
SA 40159

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/05/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8906537	27-07-89	US-A- 4837378	06-06-89
		AU-A- 3043289	11-08-89
		EP-A- 0355152	28-02-90
		JP-T- 2503004	20-09-90
FR-A- 2624736	23-06-89	None	
US-A- 4612193	16-09-86	None	
FR-A- 2333500	01-07-77	US-A- 4039662	02-08-77
		CA-A- 1071104	05-02-80
		DE-A, C 2649095	16-06-77
		JP-C- 1254263	12-03-85
		JP-A- 52070015	10-06-77
		JP-B- 59029167	18-07-84